OIPE JC140 SEP 25 2000 PATENT & TRADEMARK OFFICE

B'

the protease inhibitor is one that inhibits the cell activation activity of a composition produced by homogenizing pancreatic tissue in buffer at pH about 7 to about 8 and removing particulates.

REMARKS

A check for a three month extension of time and executed Small Entity Statements accompany this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 10-24, 32-36 and 38 are presently pending in this application. Claim 19 is amended herein to clarify that the intended treatment is in addition to the recognized or routine treatment for a disease, but is administered in addition to such treatment.

Claims 10-18, 32-36 and 38, which are directed to non-elected subject matter are retained to provide the Office an opportunity to reconsider the propriety of the restriction requirement. As discussed below, if the requirement as between groups II, III and VI is maintained, the Office is precluded from holding obviousness-type double patenting as between applications and patents that each claim the subject matter of one of these groups.

Claims 1-9, 25-31, 39 and 40, which are also directed to non-elected subject matter, are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional applications to the non-elected subject matter.

REQUIREMENT FOR RESTRICTION

The finality of the restriction requirement is noted. It is noted that Group II, claims 10-18, directed to methods of improving treatment outcome or reducing risk of treatment by administering cell activation lowering therapy, and elected group III, methods of improving treatment outcome or reducing risk of treatment by administering cell activation lowering therapy, where the therapy is administration of a protease inhibitor; and Group VI, claims 32-36 and 38,

OIPE
SEP 25 2000
PATENT & TRADEMARK OFFICE
JC140

directed to methods of diagnosis and treatment by assessing cell activation, and if elevated, administering cell activation lowering therapy. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Since, if restriction is required by the Office double patenting cannot be held, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

If the requirement is maintained, applicant can obtain three patents: one directed to methods of improving treatment outcome or reducing risk of treatment by administering cell activation lowering therapy; and a second directed to methods of improving treatment outcome or reducing risk of treatment by administering cell activation therapy, where the cell activation lowering agent is a protease inhibitor; and a third directed to methods of diagnosis and treatment by assessing cell activation and then administering cell activation lowering therapy. If, for example, the second patent issues first, the Office will be precluded from holding obviousness-type double patenting as between the first issuing patent and a later issuing patent with claims to methods of improving treatment outcome or reducing risk of treatment by administering cell activation lowering therapy, Similarly if the claims to Group I issue first, a later issuing patent with claims of group VI directed assessing cell activation and then administering cell activation lowering therapy cannot be held to be obviousness-type double patenting over the earlier issuing claims.

Applicant has retained claims 10-18, 32-36 and 38 in this application to provide the Office the opportunity to reconsider the propriety of the restriction requirement. If the Office does reconsider the propriety of the requirement as between any of groups II, III and VI, and examines any these claims; the Office is reminded that Office Action cannot be made final. If the Office does not reconsider the propriety of the requirement, the claims will be cancelled and prosecuted in separate applications; the Office will be precluded from requiring the filing of terminal disclaimers.

REQUEST FOR SUBSTITUTE SPECIFICATION

Applicant respectfully requests deferral of provision of the substitute specification. The amendments in the Preliminary amendment only correct minor and obvious typographical errors, and are not critical to prosecution of the application. A substitute specification with the amendments entered and marked up copy of the specification will be provided under separate cover.

In addressing the Office Action, it is assumed that the amendment of claim 20 inserting the word "inhibitor" in the claim has been entered.

THE REJECTION OF CLAIMS 19-24 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 19-24 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because:

> Claim 19 claims, "A method of treating or preventing disorders...", such language is not enabled by the instant specification. Such language requires undue experimentation for one of ordinary skill in the art to test to see if the protease inhibitor actually "prevents" such a disorder. The Patent Office is not equipped to test such compounds as a protease inhibitors on any and all disorders to see if they will "prevent" it. Such a claim is tantamount to a cure which has a very high standard for enablement. Applicant must show evidence on the record that they have tested the many protease inhibitors on many different disorders.

This rejection is respectfully traversed.

Prefatory to the analysis presented below, it is noted that prevention is not tantamount to a cure. It is shown in the instant application that the level of cell activation serves as a therapeutic intervention point in diseased and in healthy individuals. If cell activation levels can be lowered, then a variety of diseases, such as stroke and other ischemic events, whose onset is exacerbated or mediated by cell activation can be prevented. Preventing as stroke, for example, is not tantamount to curing a stroke. Preventing it prevents all of the devastating consequences of a stroke. Curing a stroke would involve curing all of the consequences, such as aphasia and paralysis, resulting from the stroke. Thus, prevention is not the same a cure. Cure means fixing the results of the disorder; prevention means avoiding such results. Therefore, burden of proof is not the same as urged by the Examiner.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

It is incumbent upon the examiner to first establish a prima facie case of non-enablement. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971):

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.)

Id. (emphasis in original); See also Fiers v. Revel, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, Gould v. Mossinghoff, 229 USPQ 1, 13 (D.D.C. 1985), aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C.

§ 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct").
A rejection for enablement that questions the accuracy or truthfulness of a specification can be rebutted by providing additional evidence including references published after the filing date of the application. In re Marzocchi, 439 F.2d at 223 n.4, 169 USPQ at 370 n.4 (CCPA 1971).

This case law is embodied in guidelines for examining chemical/biotechnical applications with respect to 35 U.S.C. §112, first paragraph, enablement promulgated by the Patent Office.

PTO GUIDELINES

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. Id. 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought

by the claims. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

Analysis

It is respectfully submitted that in this instance in view of the scope of the claims and data and disclosure in the specification it would not require undue experimentation to practice the claimed methods. The application is directed to methods and compositions related to the finding that the affect of treatments on many disorders can be predicted based upon the level of cell activation, and that the level of cell activation provides a diagnostic indicator and therapeutic point of intervention.

Based upon these observations and results presented in the application, treatments for a variety of disorders can be improved by also treating the subject with agents that lower cell activation. Such cell activation lowering therapy can be effected prior to commencing other treatment or in conjunction with other treatment. In addition, cell activation lowering therapy can be initiated to lower the risk of developing certain disorders, such as ischemic disorders, and also to improve outcomes.

The application also shows that a pancreatic homogenate contains cell activation inducing factors, and that the activity of these factors can be inhibited by administration of a protease inhibitor. A number of protease inhibitors are shown to be effective, and the homogenate can be used as an *in vitro* tool for identifying effective protease inhibitors. Protease inhibitors are one type of cell activation lowering therapy contemplated by the instant application.

Applying the above factors to the instant claims demonstrates that it would not require undue experimentation to practice the claimed methods.

The breadth of the claims

Claim 19 is directed to a method for improving treatment outcome or reducing risk of treatment or risk of developing disorders mediated by inappropriate cellular activation. The method involves administering a cell activation-lowering therapy, prior to or in conjunction with effecting any treatment for the disorder. In the claimed embodiments, the cell activation-lowering therapy comprises an effective amount of a protease inhibitor. The claims recites that the protease inhibitor is one that inhibits the cell activation activity of a composition produced by homogenizing pancreatic tissue in buffer at pH about 7 to about 8 and removing particulates.

Dependent claims specify that the protease inhibitor is a serine protease inhibitor (claim 22), specify particular protease inhibitors (claims 23 and 24), and particular disorders (claim 25).

Hence the claims are directed to methods for lowering cell activation by administering a protease inhibitors. As a result of treatment for cell activation the outcome of treatment for a particular disorder is improved or the risk of developing the disorder is reduced. The specified protease inhibitor is one that has a particular activity, which can be readily identified.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986). The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, further evidences the high degree of skill in the art.

The amount of direction and guidance presented, teachings in the specification and presence of working examples

The specification provides a substantial amount of guidance and includes a number working examples with *in vitro* and *in vivo* data demonstrating the effectiveness of a variety of protease inhibitors in lowering cell activation. The specification also provides assays for identifying effective protease inhibitors. As amended, the claims include a functional limitation describing the activity the such inhibitors must exhibit. In addition, the claims recite the protease inhibitors

are used to lower cell activation, and to thereby improve treatment outcomes or reduce the risk of treatment or reduce the risk of developing disorders in which cell activation is a mediator or is involved.

As shown in the application the level of cell activation, particularly neutrophil activation, is an indicator of therapeutic outcome and also serves as therapeutic target. The specification provides *in vitro* and *in vivo* data demonstrating that the level of cellular activation plays a critical role in the outcome of various disease states and that treatment with cell activation lowering agents can improve treatment outcomes of disorders, and also prevent the disorders. The specification also shows that cellular activation is an effective therapeutic target and demonstrates that protease inhibitors can lower cell activation.

The specification shows (see, *e.g.*, Example 7) that the neutrophils are implicated in the pathogenesis of a number of disease processes acute and chronic and their inappropriate upregulation (cell activation) is a predisposing risk factor for disease in otherwise healthy individuals.

As shown in the specification, plasma taken from animals and clinically after ischemic events display the ability to activate naive neutrophils, indicating that a circulating humoral factor is in part responsible for the upregulation of neutrophils and inflammation seen after these events. The presence of such an activator in rat shock plasma, is identified in the application and shown to be produced endogenously by the pancreas, which, alone of all organs studied, possesses an inherent ability to activate neutrophils *in vitro*. Further studies characterize properties of this factor *in vitro* and *in vivo*, and many of the physiological properties of the pancreatic neutrophil activator(s) have been determined.

The specification (see Examples) also shows that a pancreatic homogenate is a potent cell activator and that activation is inhibited by addition of protease inhibitors. The homogenate is shown to serve as a screening tool

for identifying agents that inhibit cell activation, including proteases (see, *e.g.*, pages 29-33). As shown in the application, when incubated with homogenates of other organs, the pancreatic homogenate supernatant, and also trypsin and chymotrypsin, cause cell-activating factors to be released from these other homogenates. Serine protease inhibitors and others that were tested inhibit production of the cell activating factors in *in vitro* experiments and reduce systemic responses *in vivo*. Other experiments showed that other tissues could be made excitatory towards neutrophils by the addition of limited concentrations of pancreatic homogenate or serine proteases.

Protease inhibitors are shown in the application to mitigate neutrophil activation *in vitro* and *in vivo* in animals. Mortality in animals subjected to either SAO shock or injected with pancreatic homogenate was reduced by treatment with a protease inhibitors. A number of protease inhibitors were studied for their ability to inhibit pancreatic homogenate-induced neutrophil activation and shown to be active. As shown in Example 7 in the specification, administration of protease inhibitors as assessed by neutrophil pseudopod formation by rat pancreatic homogenate, resulted in a decrease in neutrophil activation that varied depending on protease inhibitor used.

As a control set of experiments, sub-activating concentrations of pancreatic homogenate were added to other organ homogenates liver, spleen, intestine, and heart that had previously shown little neutrophil activating ability. Surprisingly, incubation of these tissues with low concentrations of pancreatic homogenate resulted in their ability to strongly activate neutrophils. Further experiments demonstrated that this ability to activate neutrophils by previously inert organ homogenates could be duplicated by the addition of the pancreatic proteases chymotrypsin or trypsin. Neither chymotrypsin nor trypsin intrinsically activate neutrophils *in vitro*, and heart, liver, spleen, and intestine homogenates have been shown to be non-stimulatory toward neutrophils. The addition of the

proteases, however, resulted in the ability of these tissues to activate neutrophils *in vitro*. Hence, protease inhibitors should prevent this effect.

To relate the *in vitro* results obtained with pancreatic homogenate on neutrophil activation and its inhibition by proteases to the *in vivo* state, the SAO shock experiments were repeated using Futhan pretreatment. After optimal concentration and infusion parameters were determined, 60 minutes pretreatment of Futhan was found to mitigate the decrease in mean arterial pressure (MAP) seen after reperfusion (unclamping) in SAO shock. Mortality was reduced acutely and plasma levels of peroxide production were significantly lower than in saline-treated control rats. The mechanism of protection by Futhan appears to be due to a number of factors, including reducing neutrophil activation *in vivo*, stabilization of pancreatic lysosomal and acinar membranes, and an overall increase in the protective circulating anti-protease screen.

Injection of filtered pancreatic homogenate into animals closely simulated the MAP of the reperfusion phase in SAO shock, and resulted in increased circulating peroxide production as well immediate death, as seen in SAO shock. Pretreatment of animals with Futhan increased MAP in response to pancreatic homogenate injection and **abolished** the mortality seen in untreated animals, demonstrating that protease inhibitor treatment can improve treatment outcomes. Injection of the low-molecular weight component of pancreatic homogenate also resulted in a sharp decrease in MAP. Blood pressure in these animals however, recovered after an approximately 10 minute hypotensive period and animals **did not go into shock** at the concentrations given (a maximum of 30% of the low-molecular weight component of one pancreas/animal).

These results and other in the specification demonstrate that administration of protease inhibitors results in a lowering of cell activation, which appears improve outcomes in various disorders.

Predictability

The claims are directed to methods in which cell activation is the therapeutic target by administration of a protease inhibitor that has activity in an *in vitro* assay shown in the application to correlate with *in vivo* activity in animal models, it is possible to predict which protease inhibitors to select for use in lowering cell activation

Conclusion

Therefore, in light of the scope of the claims, which are tailored to the scope of the disclosure, the extensive description in the application, the *in vitro* and *in vivo* data provided in the specification and the high level of skill of those in this art, it would not require undue experimentation to practice the methods as claimed. Furthermore, it would be unfair and unduly limiting to limit the claims to only the specifically disclosed peptides and specifically recited portions thereof. "The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions is it does the granting of more specific claims on more specific inventions" *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

In this instance, applicant is providing a general method for improving treatment outcomes and reducing treatment risks and risks of developing certain disorders, which have a common underlying etiology and therapeutic target. To limit the claims to a specific protease inhibitor, would permit those of skill in the art to practice the claimed method, but avoid infringement, merely by substituting a different protease, which could be readily identified using the methods described in the specification.

THE REJECTION OF CLAIMS 19-24 UNDER 35 U.S.C. §102

Claims 19-24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350), Okada *et al.* ((1991) *Journal of International Medical Research*

19:234-236), Yanamoto *et al.* or Yonekura *et al.* because applicant is allegedly claiming a method of treating or preventing disorders using a protease inhibitor and each of the references discloses the use of Futhan, also known as nafamostat mesylate and FUT- 175 to treat diabetes, disseminated intravascular coagulation and cerebral infraction, see abstracts. This rejection is respectfully traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The claims

Claim 19 is directed to a method for improving treatment outcome or reducing risk of treatment or risk of developing disorders mediated by or involving inappropriate cellular activation. The method involves administering a cell activation-lowering therapy, prior to or simultaneous with effecting any treatment for the disorder. In the claimed embodiments, the cell activation-

lowering therapy comprises an effective amount of a protease inhibitor. The claims recites that the protease inhibitor is one that inhibits the cell activation activity of a composition produced by homogenizing pancreatic tissue in buffer at pH about 7 to about 8 and removing particulates.

Dependent claims specify that the protease inhibitor is a serine protease (claim 22), specify particular proteases (claims 23 and 24), and particular disorders (claim 25).

Differences between the claims and the disclosure of the cited reference

Okada *et al.*

Okada *et al.* ((1991) *Journal of International Medical Research 19*:234-236)

Okada *et al.* discloses that Futhan inhibits complement activation associated with islet cell surface antibody in children with insulin-dependent diabetes mellitus soon after the onset of the disease.

Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350)

Okada *et al.* presents a study of the effect of Futhan on complement activation in an adult male with insulin-dependent diabetes mellitus and provides further evidence of complement activation in insulin-dependent diabetes mellitus.

Thus, the Okada *et al.* references disclose that complement activation is involved in insulin-dependent diabetes mellitus; Okada *et al.* also disclose that Futhan is a known inhibitor of complement activation. Okada *et al.* does not teach or suggest that the outcome of treatment for diabetes mellitus or the risks of the disease or outcome of treatment can be improved by lowering cell activation or that Futhan or any other protease inhibitor lowers the level of cell activation and that such lowering effect is a therapeutic target.

As described in the application cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes

are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces.

The instant claims are directed to methods for improving treatment outcome or reducing risk of treatment or reducing the risk of developing disorders that involve inappropriate cellular activation by administering in conjunction with other therapy or prior to other therapy a protease inhibitor in order to lower cell activation. The treatment contemplated by the instant claims is thus a treatment that reverses or prevents the changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets, such as increased stickiness, changes in shape and other characteristic changes of activated cells.

Neither Okada *et al.* reference teaches or suggests a method for reducing cell activation nor that administering cell activation lowering therapy prior to administering treatment for a particular disease or disorder has any effect on treatment outcomes or treatments for a particular disorder. Neither reference discloses or suggests that Futhan can be used to lower cell activation.

Therefore, neither Okada *et al.* reference anticipates any of the claims.

Yanamoto *et al.*

Yanamoto *et al.* reports the therapeutic effect of Futhan for treating cerebral vasospasm. Yanamoto *et al.* does not disclose or suggest that Futhan is effective for lowering cell activation, nor does no Yanamoto *et al.* disclose or suggest a method for improving outcome or treatment of a disorder or lowering the risk of developing the disorder by lowering cell activation by administering a protease inhibitor.

Since Yanamoto *et al.* does not disclose the use of Futhan alone or in conjunction with any other treatment for lowering cell activation, nor a method of treatment in which Futhan is used for lowering cell activation prior to or in

conjunction with another treatment, Yanamoto *et al.* does not anticipate any of claims 19-24.

Yonekura *et al.*

Yonekura *et al.* discloses the effects of treatment of disseminated intravascular coagulation (DIC) with nafamostat mesylate (Futhan). Yonekura *et al.* discloses that Futhan inhibits proteinases of the coagulation, fibrinolysis, Kallkrein kinin and complement systems.

The reference does not disclose use of Futhan or any protease inhibitor for lowering cell activation nor for a method of treatment in which Futhan or any other protease inhibitor is administered to lower cell activation in conjunction with treatment for a particular disorder or as a preventive of such disorder or to improve the outcome of treatment for the disorder. Therefore, Yonekura *et al.* does not anticipate any of claims 19-24.

* * *

In view of the above, examination of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE

By: _____
Stephanie Seidman
Registration No. 33, 779

Attorney Docket No. 24730-2202
Address all correspondence to:
Stephanie Seidman
HELLER EHRMAN WHITE & McAULIFFE
4250 Executive Square, 7th Floor
La Jolla, California 92037
Telephone: 858 450-8400
Facsimile: 858 587-5360
email:sseidman@HEWM.com